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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DEJONG, ERIC S	
ART UNIT	**PAPER NUMBER**
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,873	CHAN ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-24 and 27-56* is/are pending in the application.

4a) Of the above claim(s) *2,17-20;36-55 and 57-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-16,21-24,27-35 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 7-16, 21-24, 27-35, and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to use the claimed invention one of skill in the art must be able to modify a recipient polypeptide that binds a target by replacing an identified set of amino acid residues within said polypeptide with an identified spatially conserved protease

motif, such that the engineered polypeptide would retain both of said binding and protease activities. For reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b) The disclosure provides methods and procedures for carrying out *in silico* modeling of a recipient polypeptide to contain a spatially conserved protease motif. The instant disclosure further provides guidance for testing for proteolytic activity in a polypeptide. However, the disclosure does not provide detailed guidance on how to computationally model a polypeptide to contain a protease motif such that the modeled polypeptide, when synthesized, will retain the predicted protease activity.

c) The disclosure provides examples of computationally identifying proteolytic sites that are suitable for engineering into a similar geometric region of a recipient polypeptide. The instant disclosure further provides guidance for testing for proteolytic activity in a polypeptide. However, the instant disclosure does not provide working examples wherein a computationally modeled polypeptide containing a protease motif was further synthesized and demonstrated to maintain a predicted protease activity.

d) The nature of the invention, modeling and engineering polypeptides to introduce a an active protease domain, is extremely complex.

e) The prior art shows that prediction of structure and activity in polypeptides can be reliably accomplished only if very close homologs of known structures are available and if said homologs further share high degrees of structural, sequence and activity similarity. A recent review of protein modeling and structure prediction provided by Ginalski et al. published on states:

> "Theoretically, it should be possible to deduce structure from sequence by accurate simulation of physical processes. We are very far from achieving this goal, and the methods of practical importance were traditionally based on the observation that proteins with similar sequences are structurally similar as well." (Ginalski et al., page 1874, column 1, line 15 through column 2, line 5)

and

> "Predicted protein structures can be used if very close homologs with known structure are available... Currently available structure prediction methods do not allow for high-quality predictions of the quaternary structure of protein complexes and for the prediction of interactions between proteins. Current benchmarks indicate that methods predicting interactions can be successful mainly in cases when structures exhibit minimal conformation changes upon complex formation. Substantial errors observed in predicted models go beyond the limits tolerated by such methods." (Ginalski et al., page 1887 column 1, line 45 through column 2, line 2).

The instantly claimed method only requires that a recipient polypeptide have a set of amino acid residues that match a spatially conserved motif derived from a separate set of amino acids residues from a protease motif. The instant claims do not set forth a requisite level of matching such that the overall structure of recipient polypeptide, following the substitution of the amino acids derived from a protease domain, will exhibit only minimal conformational changes. Further, the instantly claimed method does not require any sequence similarity between an original set of amino acids native to a recipient polypeptide and the set of amino acids derived from a protease motif that is to be substituted into said recipient polypeptide. Further, the instantly claimed method does not require any similarity in the activity between the original set of amino acids native to a recipient polypeptide and the set of amino acids derived from a protease motif that is to be substituted into said recipient polypeptide .

f) The skill of those in the art of polypeptide modeling and structure prediction is extremely high.

g) The predictability of successfully engineering a polypeptide to contain an

active protease domain is unknown in the art. Successful applications of predicting protein structure and activity have been identified in the art for cases where very close homologs were available that further maintained high sequence, structure, and activity similarity.

h) The claims are broad in that they encompass engineering spatially conserved protease motif into a generic recipient polypeptide.

The skilled practitioner would first turn to the instant disclosure for guidance in using the claimed invention. However, the disclosure does not provide detailed guidance on how to model polypeptides containing a protease motif such that the modeled polypeptides, when synthesized, will reliably retain the predicted protease activity. As such, the skilled practitioner would turn to the prior art for such guidance, however the predictability of successfully engineering a polypeptide to contain an active protease domain is unknown in the art. Finally, said practitioner would turn to trial and error experimentation to determine if a polypeptide engineered to contain an active protease domain actually maintains said protease activity when synthesized. Such amounts to undue experimentation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-5, 7-16, 21-24, 27-35, and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 21 each recite the limitation "testing for catalytic activity the recipient polypeptide substituted with the first set of amino acid residues making up said protease motif" in lines 13 and 14 of claim 1, lines 14 and 15 of claim 21. Similarly, Claim 56 recites the limitation "testing for catalytic activity the recipient polypeptide or polypeptide complex substituted with the first set of amino acid residues making up said protease motif" in lines 15 and 16 of said claim. However, the previously recited substitution step of "substituting said second set of amino acid residues in said recipient protein with the first set of amino acids residues making up said protease motif" (see for example lines 10-13 of instant claim 1) may be performed either *in silico* or on real world molecules. This causes the metes and bounds of the instant claims to be indefinite because in embodiments wherein said substitution step is performed *in silico*, the resultant recipient polypeptide embodies only a computer representation and it is unclear how a physical step drawn to testing for catalytic activity can be performed on a computer representation of said recipient polypeptide. Claims 3-5, 7-16, 22-24, and 27-35 are also included under this rejection due to their dependence of either of claims 1 or 21.

Claims 1, 21, and 56 each recite the limitation "testing for catalytic activity" in line 13 of claim 1, line 14 of claim 21, and line 14 of claim 56. This causes the metes and bounds of the instant claims to be indefinite because it is unclear is the recited "testing for catalytic activity" refers only to testing for protease activity of a recipient polypeptide modified to contain a protease motif (see for example, lines 10-12 of claim 1) or, alternatively, if said testing step is open to testing for catalytic activities other than protease activity. Claims 3-5, 7-16, 22-24, and 27-35 are also included under this rejection due to their dependence of either of claims 1 or 21.

For the purpose of continuing examination, the limitation "testing for catalytic activity" has been construed to read only on testing for protease activity.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 3-5, 7-16, 21-24, 27-35, and 56 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1, 3-5, 7-16, 21-24, 27-35, and 56 are drawn to a method of engineering a spatially conserved protease motif into a recipient polypeptide. The instantly claimed process comprises the steps of obtaining a spatial relationship for a first set of amino acids, identifying a second set of amino acid residues in a recipient polypeptide, and substituting said second set of amino acids into a recipient polypeptide involving algorithmic and computational procedures, and, therefore, involves the application of a

judicial exception. Regarding inventions involving the application of a judicial exception, said application must be a practical application of the judicial exception that includes either a step of a physical transformation, or produces a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)).

The instant claims have been amended to further recite a step drawn to testing for catalytic activity the recipient polypeptide substituted with a first set of amino acids making up a protease motif (see for example, lines 13 and 14 of instant claim 1). However, the previously recited step of "substituting said second set of amino acid residues in said recipient polypeptide with the first set of amino acids residues making up said protease motif" (see for example lines 10-13 of instant claim 1) may be performed either *in silico* or on real world molecules. Embodiments of the claimed method wherein a real world recipient polypeptide is generated from the recited substitution step and said real world recipient polypeptide is further tested for catalytic activity are statutory. However, for *in silico* embodiments of the claimed method wherein a computer representation of said recipient polypeptide is generated from said substitution step, the recited step of testing for catalytic activity would be performed on data representing a simulation of a recipient polypeptide. Therefore, for these *in silico* embodiments, no physical transformation would result from practicing the claimed method, thus the Examiner must determine if these embodiments of the claimed process produces a useful, concrete, and tangible result.

In determining if an application of a judicial exception produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a result to be "useful," the application of a judicial exception must produce a result that is specific, and substantial. For a result to be "concrete," the application of a judicial exception must have a result that is reproducible. For a result to be "tangible," the application of a judicial exception must produce a real world result . Furthermore, the claim must be limited only to statutory embodiments.

Claims 1, 3-5, 7-16, 21-24, 27-35, and 56 do not produce a tangible result. For *in silico* embodiments of the claimed method, no physical transformation would result from practicing the claimed testing step. Further the instant claims lack a limitation wherein said substitution or testing steps result in a tangible result, such as a result being output to a display, a user, a readily accessible memory or other computer on a network. A tangible result requires that the claim must set forth a practical application of a judicial exception to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result is outputted to a display, a user, a readily accessible memory or other computer on a network.

Response to Arguments

Applicant's arguments filed 12/27/2006 have been fully considered but they are not persuasive.

In regards to the rejection of claims under 35 USC § 101 as being drawn to non-statutory subject matter, applicants argue that independent claims 1, 21, and 56 have

been amended to introduce a step that requires a "physical transformation", i.e. testing the engineered polypeptides for activity, thereby obviating the non-statutory subject matter rejection.

In response, it is acknowledged that the instant claims have been amended to further recite a step drawn to testing for catalytic activity the recipient polypeptide substituted with a first set of amino acids making up a protease motif (see for example, lines 13 and 14 of instant claim 1). However, the previously recited step of "substituting said second set of amino acid residues in said recipient polypeptide with the first set of amino acids residues making up said protease motif" (see for example lines 10-13 of instant claim 1) may be performed either *in silico* or on real world molecules. Embodiments of the claimed method wherein a real world recipient polypeptide is generated from the recited substitution step and said real world recipient polypeptide is further tested for catalytic activity are statutory, as argued by applicants. However, for *in silico* embodiments of the claimed method wherein a computer representation of said recipient polypeptide is generated from said substitution step, the recited step of testing for catalytic activity would be performed on data representing a simulation of a recipient polypeptide. Therefore, for *in silico* embodiments of the claimed method, no physical transformation would result from practicing the claimed testing step. Further the instant claims lack a limitation wherein said substitution or testing steps results in a tangible result, such as a result being output to a display, a user, a readily accessible memory or other computer on a network. Therefore the instant claims are not limited only to statutory subject matter.

In regards to the rejection of claims under 35 USC § 112, 1st paragraph, applicants argue that the cited prior art actually supports the enablement of the claimed invention and that a skilled artisan need not conduct any undue experimentation because the recipient polypeptide of the claimed invention can well tolerate the minimal perturbation to its over all structure.

In response, it is reiterated from the above rejection that the prior art of Ginalski et al. shows that prediction of structure and activity in polypeptides can be reliably accomplished only if very close homologs of known structures are available and if said homologs further share high degrees of structural, sequence and activity similarity. The instant claims do not require any sequence homology between the amino acid residue set derived from a protease motif and the substituted amino acid residue set within said recipient polypeptide. While applicants argue that the recipient polypeptide of can well tolerate the minimal perturbation to its over all structure, there are no limitations recited in the instant claims that limit the number of amino acids residues substituted into a recipient polypeptide or the positions that said substituted residues would occupy such that there would be only a minimal perturbation to the overall structure. The prior art of Ginalski et al. sets forth that currently available structure prediction methods do not allow for high-quality predictions and these methods give rise to substantial errors. Further, the instantly claimed method requires only a geometric relationship that matches a conserved geometry. This contrasts with the successful application of structure prediction and modeling of proteins set forth in the prior art wherein high similarity in sequence, structure and activity is emphasized.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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19 March 2007

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER